UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/658,283	09/08/2000	C Alexander Turner Jr	LEX-0041-USA	3550

24231 7590 04/06/2004

LEXICON GENETICS INCORPORATED
8800 TECHNOLOGY FOREST PLACE
THE WOODLANDS, TX 77381-1160

EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/658,283	TURNER JR ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/4/2004 has been entered.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 6-9 are rejected, under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility, for reasons of record set forth the Office action sent 7/1/2002 and 12/26/2002. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

According to MPEP § 2107, a rejection for lack of utility is imposed when an invention lacks an asserted specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility. An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible.

The rejection of record set forth that the nucleic acid encoding the NGPCR polypeptide has been isolated because of its similarity to known proteins. However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors and that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Additionally, the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. The instant claims are drawn to a nucleic acid encoding a polypeptide that has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as NGPCR, the instant invention is incomplete. The polypeptide encoded by the nucleic acids of the instant invention is known to be structurally analogous to proteins that are known in the art as G protein coupled receptors. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ a protein of the instant invention in

the identification of substances which inhibit its activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for NGPCR then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

The Doerks reference was cited to show that it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors. Applicant argues that the Doerks reference addresses functional predictions based on sequence comparisons to unknown proteins. However, Doerks discuses several proteins which have had their function predicted based on homology to known proteins, for example, an assignment error was made for proteins gil2314657 and gil2688341 based on significant similarity to proline dipeptidases, when this assignment was based on similarity of a region that was not the active site (page 248column 3, third full paragraph)

The rejection of Paper No. 10, 7/1/2002 further set forth that even if the NGPCR protein is found to be a G-protein coupled receptors, they are orphan receptors. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the NGPCR protein, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. Applicant argues that the encoded amino acid sequence is 93% identical to a sequence reported in GenBank as a VIGR GPCR (GenBank AAO13250) and that therefore one of skill in the art would conclude that SEQ ID NO: 2 is a novel GPCR and thus meets the requirements under 35 USC § 101. However, the

annotated protein has not been shown to function as a GPCR, and the art recognizes the assignment of function based on homology is inherently difficult, as evidenced by the references of Doerks, Brenner and Bork. Additionally, Yan et al. teaches that in certain cases, a change of two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000, page 525, Figure 2A). This 2 amino acid change is out an amino acid of 154 amino acids, thus even proteins that only have a 1.3% difference can bind different ligands.

According to MPEP 2107, in order for Applicant to rebut the rejection for lack of utility imposed because the invention lacks an asserted specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility, Applicant must provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. In the instant case, even if the AAO13250 polynucleotide is found to function as a GPCR, the date of publication of the sequence is December 31, 2002, which is after the filing date of the instant application. In order for an asserted utility to be well-established, it must be well-established at the time of filing. Since the AAO13250 polynucleotide is a post-filing reference, the asserted utility was not well-established at the time of filing.

Further according to MPEP 2107, the examiner should also ensure that there is an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. That is, the applicant has the burden to establish a probative relation between the submitted evidence and the originally disclosed properties of the claimed

invention. In the instant case, at the time of filing the instant nucleic acids were not disclosed as encoding specifically VIGR GPCRs, but only described as encoding generically as GPCR's (see Specification at 2, lines 6-20). There are many types of GPCRs, including, *inter alia*, receptors for epinephrine, norepinephrine, dopamine, histamine, and eicosanoids. The fact that the Specification only describes the encoded polypeptide as a GPCR demonstrates that at the time of filing, Applicant did not know the type of GPCR, if any, the encoded polypeptide would make. Since the originally disclosed properties of the claimed invention are only set forth as encoding a GPCR, there is not a probative relationship between the submitted evidence of the encoded polypeptide allegedly functioning as a GPCR, and the disclosed properties of the encoded polypeptide being a VIGR GPCR. Applicants argue that the AAO13250 sequence is nearly 93% identical to the encoded SEQ ID NO: 2 and thus demonstrates the utility of the claimed polynucleotide. However, as noted above, the annotation of the AAO13250 sequence as a GPCR was published post-filing, and thus the utility was not well-established at the time of filing, and furthermore, there is not a probative relation between the submitted evidence and the originally disclosed properties of the claimed invention, since the encoded polypeptide was only described as an GPCR, not a VIGR GPCR. In addition, it is not clear that the AAO13250 polypeptide was ever demonstrated to be a GPCR, which is exactly the situation the Doerks reference was cited to show. The Doerks reference teaches that inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Thus, while Applicant is relying on the AAO13250 polypeptide to show the utility of the claimed encoding polynucleotide, it is not clear that the function of the AAO13250 polypeptide is actually known, since the Doerks reference is

relevant as it teaches that sequence-to-function methods of assigning protein function are prone to errors.

Applicant further argues that the production of a knockout mouse demonstrated that the polynucleotide of SEQ ID NO: 2 encoded a protein which was involved in regulation of systolic blood pressure, and that the polynucleotide would thus have a utility in finding compounds to treat heart disease and abnormal blood pressure. However, there are two problems with this alleged utility. First, the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). The results of the knock-out mouse experiments are not in the Specification, nor were they presented as a Declaration. Secondly, Applicant must provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well-established at the time of filing. In the instant case, the results of the knock-out mouse experiments are not in the Specification, and thus one of skill in the art would not have recognized the specific and substantial utility at the time of filing.

Applicant further argues that the claimed nucleic acid sequence have utility in assessing gene expression in a DNA array or gene chip, and cites several issued U.S. patents covering the gene chip technology. However, use of the claimed polypeptide in an array for selectivity screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility that would apply to virtually ever member of a general class of materials, such as any collection of DNA. Even if the expression of Applicant's individual polynucleotide is affected by a test compound in an array for drug screening, the

specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotide has no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what use any expression information regarding this polynucleotide could be put. Despite Applicant's arguments, this is not a confusion of a specific utility with the alleged need for a "unique" utility. Any nucleotide sequence can be put on a DNA array and then this array can be screened to determine whether the expression pattern correlates with a disease state or condition. This is not a specific utility for this nucleic acid. A specific utility for this nucleic acid would be a correlation between expression of the specific nucleic acid in a disease state or some other condition that would be useful to know. That has not been demonstrated here.

Applicant further argues that the claimed polynucleotide sequences have utility in "determining the genomic structure", "identification of protein coding sequence", and "identification of exon splice junctions" and provide biologically validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes exon sequence. Applicant newly cites the Venter reference to allegedly demonstrate the significance of expressed sequence information in the structural analysis of genomic data.

This has been fully considered but is not deemed to be persuasive because such a utility is considered a research utility only designed to identify a particular function of the claimed sequences and is not a substantial utility. See, e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966) wherein a research utility was not considered a "substantial utility." While the Examiner agrees with the Applicant on the scientific value of the claimed polynucleotide

sequences and on the significance of expressed sequence information in structural analysis of genomic data, such a use of the polynucleotide sequences in gene mapping does not represent a specific and substantial utility. The exhibit and the publication cited by the Applicant merely show that the significance of expressed sequences in the structural analysis of genomic data; they do not show that the present polynucleotide sequences have a patentable utility.

Citing case law, Applicant urges that the present claims clearly meet the requirement of 35 U.S.C. §101. The essential disagreement appears to be the interpretation of what constitutes a specific, substantial and credible utility.

Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. First, the statement, "(t)o violate §101 the claimed device must be totally incapable of achieving a useful result." Brooktree Corp. v. Advanced Micro Devices, Inc., 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), indicates that a rejection under 35 U.S.C. § 101 for lack of operability can be overcome by a showing of actual use or commercial success. The claimed invention in the instant case is drawn to nucleic acid sequences, not a device; the instant rejection under 35U.S.C. §101 is not directed to inoperativeness of a device, rather to a lack of patentable utility of the claimed nucleic acid sequences; and the instant issue is whether the asserted utilities meet the three-pronged test for a patentable utility.

Secondly, since the specification fails to disclose a specific, substantial utility or a well-established utility, the present claims do not satisfy the utility requirement of 35 U.S.C. §101. Merely citing case laws on the utility requirement does not render a patentable utility for the present invention. While "anything under the sun that is made by man" is patentable, it does not

necessarily mean the present invention is patentable. In fact, the present invention is not patentable due to lack of a patentable utility.

Furthermore, while the FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, and the requirement for the utility of the claimed invention is different from the FDA standard for drug approval, 35 U.S.C. §101 does require a specific, substantial, and credible utility, or well-established utility for an invention. Such a utility has to be a "real world " context of use which does not require significant further research. Applicant confuses this requirement with the "further research and development" needed in pharmaceutical composition and drug development. In other words, a patentable utility has to be clearly identified or immediately apparent in the specification, whereas some "further research and development" is permitted in drug development. For example, determining optimal dosages or drug tolerance in human is further research and development, which is acceptable under 35 USC 101 because it is not significant. On the other hand, determining a specific disease to be treated by a drug constitutes significant further research and development, which is not acceptable under 35 U.S.C. §101.

In the instant case, the specification fails to disclose the biological functions, physiological significance, or any specific and substantial utility of the claimed molecules. Without such information, how can one in the skilled art use the claimed invention in a meaningful manner? See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Applicant has cited several issued patents, however, each Application is examined on its own merits.

Claims 7, 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 1, does not reasonably provide enablement for in vivo transfection.

The specification on page 25 discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, including cells within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 1 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as written are not enabled. This rejection could be overcome by addition of the limitation wherein the host cells are isolated.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
March 25, 2004